REMARKS

The Invention

The present invention relates to methods for increasing the efficiency of the transfection of cycling cells. The methods involve synchronizing cells at a first stage of the cell cycle, and transforming the cells at a second stage of the cell cycle within about one cell cycle of the first stage with a nucleic acid. The invention further relates to cancer therapy and, in particular, to methods of efficiently transfecting cancer cells with nucleic acids.

Status of the Claims

Applicants wish to thank Examiner Woitach for extending the courtesy of the telephonic interview held on June 20, 2001 with Applicants' representatives Eric Baude and Eugenia Garrett-Wackowski. During this interview, a number of issues were clarified which have helped Applicants to more fully address the concerns of the Examiner. Applicants thank Examiner Woitach for his time.

Claims 38-44 and 46-77 were pending. Claims 38-44 and 46-77 were examined and stand rejected. Applicants have canceled claims 55-68 without prejudice or disclaimer. Applicants have amended claims 38, 69, 74 and 77. The amendments do not introduce new matter or raise new issues that would require further consideration and/or search. As amended, claims 38, 69, and 74 recite that the cell cycle blocking agent is a member selected from the group consisting of "taxol, taxolene, and a vinca alkaloid." Support for this amendment is found throughout the specification, for example on page 24, table 1. Claim 38 has also been amended to recite "introducing a nucleic acid comprising a foreign therapeutic gene into a cell in a patient." Support for this amendment is found throughout the specification, for example on page 4, line 23 to page 5, line 24. Claim 69 has also been amended to recite "inhibiting growth of cancer cells in a patient having a cancer." Support for this amendment is found throughout the specification, for example on page 18, lines 9-25. Claim 74 has also been amended to recite "wherein said nucleic acid is administered in a lipid formulation comprising a cationic lipid and a lipid derivative." Support for this amendment is found throughout the specification, for example on page 27, lines 11-18. Claim 74 has further been amended to recite "treating a patient having a cancer." Support for this amendment is found throughout the specification, for example on page 17, lines 18-25. Thus, no new matter is added by these amendments.

New claims 78-84 have been added. New claims 78 and 80-82 find support in the specification on page 27, lines 5-10, which recites that stable plasmid-lipid particles can be formulated using the methods and compositions set out in U.S. Patent No. 5,705,385. The '385 patent was specifically incorporated by reference on page 27, line 10. The '385 patent describes the claimed methods of formulating the lipid-nucleic acid particles of claims 78 and 80-82 at, *inter alia*, col. 8, lines 52-64. New claims 79 and 83-84 find support in the specification for example on page 24, table 1. Thus, no new matter is added by these new claims.

Applicants request that the amendments of claims 38, 69, 74, and 77; the cancellation of claims 55-68; and new claims 78-84 in the present Request for Continued Examination be entered under 37 C.F.R. § 1.114. Applicants respectfully request reconsideration and continued examination of claims 38-44 and 46-54, and 69-84.

A version of the claims with markings to show changes to the claims are provided in Appendix A. All of the pending claims are provided in Appendix B for the Examiner's convenience.

Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 38-44, 46-55 and 56-77 are rejected under 35 U.S.C. § 112, first paragraph. The Examiner alleges that claims 38-44, 46-55, and 56-77 are not enabled because there is insufficient guidance in the specification to practice the claims in view of the lack of guidance, working examples, breadth of the claims, the level of skill in the art and state of the art at the time of the claimed invention, *i.e.*, it would have required one of skill in the art undue experimentation to practice the invention as claimed. The Examiner did, however, state that the specification *is enabled* for:

> a method of inhibiting the growth of cancer cells in a subject, the method comprising administering an amount of vincristine sulfate and cisplatin in an amount effective to inhibit growth of said cells at or around the site of the tumor, and administering to said cells a polynucleotide encoding a gene which is well known in the art to inhibit cell growth ... .

Applicants respectfully traverse this rejection. Applicants agree that the claims are enabled for treatment of cancer. However, Applicants also maintain that the claims are generic for introducing other nucleic acids into a cell.

As identified by the Patent Office and the Federal Circuit, the proper standard for determining whether undue experimentation is required by one skilled in the art to practice the

invention includes consideration of factors such as the amount of guidance provided in the application and the presence of working examples. *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Int. 1985); *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). Furthermore, "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should precede." *Wands*, 8 USPQ2d at 1404 (quoting *In re Jackson*, 217 USPQ 804 (Bd. Pat. App. & Int. 1982).

Claims 55-68 have been canceled without prejudice or disclaimer. Therefore, Applicants respectfully request that this aspect of the rejection be withdrawn.

Applicants maintain that claims 38, 69, and 74, as amended, are enabled given the guidance in the specification and the knowledge of those of skill in the art. Claim 38 is directed toward methods of introducing nucleic acids into cells in patients. Claims 69 and 74 are directed toward methods of treating patients with cancer.

The specification provides guidance on methods for delivering nucleic acids to cells. In addition, the specification provides several working examples of methods for delivering nucleic acids to cells. For example, the specification demonstrates that intravenous injection of tumor bearing-mice with OncoTCS (vincristine sulfate encapsulated in sphingomyelin-containing TCS) followed by intravenous injection with a luciferase-encoding-plasmid resulted in luciferase expression in the tumor (page 49, line 23, bridging to page 50, line 5). Similar results were achieved with OncoTCS and the TK/ganciclovir system with a luciferase-encoding-plasmid (see, e.g., page 54, line 27 to page 55, line 31). Furthermore, spleen cells were also targeted with OncoTCS and a luciferase-encoding-plasmid by intravenous injection (see, e.g., page 52, line 23 to page 53, line 30).

Moreover, the specification provides working examples that the claimed methods are successful in inhibiting tumor growth. For instance, tumor growth inhibition was achieved using intravenous injection of OncoTCS and a plasmid encoding IL-12 (see, e.g., page 54, lines 1-26). Targeting to tumors was also achieved with OncoTCS and a luciferase encoding plasmid to a solid tumor by intratumoral injection (see, e.g., page 51, line 10, bridging to page 52, line 21).

In addition, the specification discloses methods to specifically target the composition comprising the DNA to a cell using a targeting moiety (e.g. antibodies, proteins) to a lipid (page 32, lines 11-14). These numerous examples and the disclosure in the specification provide sufficient

guidance to one of skill in the art to carry out the claimed invention. Accordingly, Applicants respectfully request that the rejection be withdrawn.

Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 38-44 and 46-55 and 56-77 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants respectfully traverse this rejection.

> As set forth in MPEP § 2173.02, "[d]efiniteness of claim language, must be analyzed in light of (A) content of the application; (B) the teachings of the prior art; and (C) the claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made."

In the instant case, the specification adequately defines the terms or the terms are adequately understood to one of skill in the art, such that the claims are not indefinite under 35 U.S.C. §112, second paragraph. Several bases of indefiniteness were raised, and they will be discussed in turn.

a. Claims 38-44 and 46-55 and 56-77

The recitation of "cell cycle blocker" in claims 38-44, 46-55, and 56-77 is allegedly unclear. Applicants have canceled claims 56-68 and respectfully request that the rejection be withdrawn as to those claims. Applicants respectfully submit that cell cycle blocker is a term of art known and used by those of skill in the art. However, in order to expedite prosecution, claims 38, 69, and 74, have been amended, recite several cell cycle blockers in a Markush group: taxol, taxolene, vinblastine, vincristine, vinorelbine, and a vinca alkaloid. Therefore, the term "cell cycle blocking agent" is sufficiently definite as specific compounds are recited in the Markush group. Accordingly, Applicants respectfully request that the rejection be withdrawn.

b. Claims 55-68

Claims 55-68 have been canceled without prejudice or disclaimer. Therefore, this aspect of the rejection is rendered moot. Applicants respectfully request that this aspect of the rejection be withdrawn.

c. Claim 69

Claim 69 is allegedly unclear as the administration of a therapeutic gene is not limited to treatment of cancer. Claim 69 has been amended to include the phrase "inhibiting growth of

cancer cells in a patient having a cancer." Therefore claim 69 is sufficiently definite as to what is being treated in the patient having cancer. Accordingly, Applicants respectfully request that this aspect of the rejection be withdrawn.

d. Claim 70

Claim 70 is allegedly unclear because 'said cancer' has no antecedent basis in claim 69. Claim 70 is dependent on claim 69. Applicants respectfully point out that the term "cancer" appears in claim 69. Therefore, the phrase "said cancer" in claim 70 has antecedent basis in claim 69. Accordingly, Applicants respectfully request that this aspect of the rejection be withdrawn.

e. Claim 74

Claim 74 is allegedly unclear in that the claim encompasses any therapeutic effect, however the present specification primarily teaches treatment of cancer cells. Claim 74 has been amended to recite the phrase "[a] method of treating a patient having a cancer." Therefore, claim 74 is sufficiently clear as to the scope of the method. Accordingly, Applicants respectfully request that the rejection be withdrawn.

f. Claim 77

Claim 77 is allegedly vague and unclear as to what the "%" refers to and whether it is by weight, by volume or by some other reference. Claim 77 has been amended to recite that it is the steric lipid of claim 77 that is present by *weight* in an amount from about 1% to about 20% of the lipid formulation. Accordingly, Applicants respectfully request that the rejection be withdrawn.

Rejection Under 35 U.S.C. § 102(e)

Claims 38-44, 46, 47, 49, 52, 55, and 56-73 are rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Roth *et al.* (U.S. Patent 5,747,469). In making this rejection, the Examiner has alleged that the lipid formulations of Roth *et al.* inherently meet the limitation of being resistant to DNAse under the conditions recited in claim 38 and 55. Applicants respectfully traverse this rejection.

For a rejection of claims under § 102(b) or § 102(e) to be properly founded, the Examiner must establish that a single prior art reference discloses each and every element of the claimed invention. *See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 U.S.P.Q. 81 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987). In *Scripps Clinic & Research Found. v. Genetech, Inc.*, 18 U.S.P.Q.2d 1001 (Fed. Cir. 1991), the Federal Circuit held:

> Invalidity for anticipation requires that all of the elements and limitations of the claim are found with a single prior art reference. . . .***There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention.***

Id. at 1010 (emphasis added). Anticipation can be found, therefore, only when a cited reference discloses ***all*** of the elements, features or limitations of the presently claimed invention.

Claims 55-68 have been canceled without prejudice. Therefore, Applicants respectfully request withdrawal of this aspect of the rejection.

Independent claims 38 and 69 have been amended to recite "wherein said cell cycle blocking agent is selected from the group consisting of taxol, taxolene, and a vinca alkaloid." In contrast to the claimed invention, Roth *et al.* disclose contacting cells with agents such as cisplatin, doxorubicin, etoposide, verapamil, podophyllotoxin, and 5-fluorouracil (*see* col. 37, claims 4, 6, 8, 10, 11, and 12, respectively). Roth *et al.* thus fail to disclose the use of the cell cycle blocking agents of the claimed invention. Therefore, Roth *et al.* do not disclose all of the elements of the claimed invention. Accordingly, Applicants respectfully request that the rejection be withdrawn.

Rejection Under 35 U.S.C. § 102(b)

Claims 38-44, 46, 49, 52, 55, and claims 56-73 are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Son *et al.*, *Proc. Natl. Acad. Sci.* (1994), 91:12669-12672. In making this rejection, the Examiner concedes that Son *et al.* "do not disclose a specific therapeutic gene," yet alleges that "[g]iven the general guidance of both Son *et al.* and the present specification, one of ordinary skill in the art would anticipate the invention as claimed." Applicants respectfully traverse this rejection.

For a rejection of claims under § 102(b) or § 102(e) to be properly founded, the Examiner must establish that a single prior art reference discloses each and every element of the claimed invention. *See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 U.S.P.Q. 81 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987). In *Scripps Clinic & Research Found. v. Genetech, Inc.*, 18 U.S.P.Q.2d 1001 (Fed. Cir. 1991), the Federal Circuit held:

> Invalidity for anticipation requires that all of the elements and limitations of the claim are found with a single prior art reference. . . .***There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention.***

Id. at 1010 (emphasis added). Anticipation can be found, therefore, only when a cited reference discloses ***all*** of the elements, features or limitations of the presently claimed invention.

Claims 55-68 have been canceled without prejudice. Therefore, Applicants respectfully request withdrawal of this aspect of the rejection.

Independent claims 38 and 69 have been amended to recite "wherein said cell cycle blocking agent is a member selected from the group consisting of taxol, taxolene, and a vinca alkaloid." Son *et al.* teach away from the present invention. In particular, Son *et al.* disclose that ***only*** cisplatin was effective in sensitizing the cells to transfection (page 12671, right hand column, lines 13-14 and Figure 4). Moreover, Son *et al.* disclose that the vinca alkaloid vincristine had "no effect" in sensitizing cells to transfection (page 12671, right hand column, Fig. 4, left hand column). Thus, Son *et al.* fail to disclose all of the elements of the claimed invention and do not anticipate the claimed invention. Therefore, Applicants respectfully request that the rejection be withdrawn.

Rejections Under 35 U.S.C. § 103(a)

The claims have been rejected, in various combinations, under 35 U.S.C. § 103(a) over a number of different references. Applicants respectfully traverse each of the § 103 obviousness rejections.

> As set forth in M.P.E.P. § 2143, "[t]o establish a *prima facie* case of obviousness, three basic criteria must be met. *First*, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. *Second*, there must be a reasonable expectation of success. *Finally*, the prior art reference (or references when combined) must teach or suggest all the claim elements. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)."

1. Rejection of claims 38, 53, 54, and 55-73 over Roth *et al.* and Son *et al.*

Claims 38, 53, 54, and 55-73 are rejected under 35 U.S.C. § 103(a) as unpatentable over Roth *et al.* and Son *et al.* In making this rejection, the Examiner alleges that Roth *et al.* and Son *et al.* both inherently disclose the use of a DNAse resistant formulation as set forth in the claimed invention.

Claims 55-68 have been canceled without prejudice. Therefore, Applicants respectfully request withdrawal of this aspect of the rejection.

Independent claims 38 and 69 have been amended to recite "wherein said cell cycle blocking agent is selected from the group consisting of taxol, taxolene, and a vinca alkaloid."

As discussed above, Roth *et al.* and Son *et al.* do not disclose all of the elements, features or limitations of the presently claimed invention. In particular, Son *et al.* teach away from the use of drugs other than cisplatin. Son *et al.* disclose that the vinca alkaloid vincristine, which is recited in the claimed invention, had "no effect" in sensitizing cells to transfection (page 12671, right hand column, Fig. 4, left hand column). Moreover, Son *et al.* teach that other anticancer drugs such as methotrexate, etoposide, cytosine arabinonucleoside, doxorubicin, and carboplatin (a geometric isomer of cisplatin) had no effect (page 12671, right hand column). Therefore, Son *et al.* teach away from the use of the compounds recited in the claimed invention (e.g., taxol, taxolene, vinblastine, vincristine, vinorelbine, and a vinca alkaloid) and away from combining the method of Son *et al.* with the method of Roth *et al.* Even if the teachings of Roth *et al.* and Son *et al.* were combined, it would not lead to the claimed invention because the references fail to teach or suggest the use of the cell cycle blocking agents of the claimed invention. Accordingly, Applicants respectfully request withdrawal of this rejection.

2. Rejection of claims 38 and 48 over Son *et al.*, Roth *et al.*, and Walker *et al.*

Claims 38 and 48 are rejected under 35 U.S.C. § 103(a) as unpatentable over Son *et al.* Roth *et al.*, and Walker *et al.* (U.S. Patent 6,041,252). In making the rejection, the Examiner alleges that Walker *et al.* disclose the systemic delivery of agents by means of a liposome and concludes that one of skill in the art would be motivated to combine the nucleic acid and agent in one liposome for a single delivery vehicle. Applicants respectfully traverse this rejection.

Independent claim 38 has been amended to recite "wherein said cell cycle blocking agent is selected from the group consisting of taxol, taxolene, and a vinca alkaloid."

As discussed above, Son *et al.* and Roth *et al.*, alone or in combination, fail to disclose all of the elements of the claimed invention. Moreover, as discussed in detail above, Son *et al.* teach away from the claimed invention. Therefore, one of skill in the art would have no motivation to combine Son *et al.* and Roth *et al.* Walker *et al.* do not cure the deficiency of Son *et al.* and Roth *et al.* Walker *et al.* disclose the use of electrical fields to deliver therapeutic agents encapsulated in a liposome (see e.g., Abstract). Walker *et al.* contains no hint or suggestion of the

use of a cell blocker or the introduction of a nucleic acid into a cell. Therefore, one of skill in the art would not have had the motivation to combine Walker *et al.* with Son *et al.* and Roth *et al.* Even if one of skill in the art were to combine Son *et al.*, Roth *et al.*, and Walker, *et al.* the combination would not lead to the claimed invention because none of the references alone, or in combination teach or suggest the use of the cell cycle blocking agents of the claimed invention.

Absent a teaching or suggestion of the use of cell cycle blockers as disclosed and claimed in the present invention, the present invention is non-obvious, and thus, patentable. Therefore, Applicants respectfully request withdrawal of this rejection.

3. Rejection of claims 74-77 over Son *et al.*, Roth *et al.*, and Bally *et al.*

Claims 74-77 are rejected under 35 U.S.C. § 103(a) as unpatentable over Roth *et al.* and Son *et al.* as applied to claims 38, 53-73 above, and further in view of Bally *et al.* (US Patent 5,705,385). In making this rejection, the Examiner alleges that Bally *et al.* teach lipid-nucleic acid particles for the delivery and use in gene transfer, in particular the use of PEG-lipid derivative and a G_{M1}-modified lipids to prevent particle aggregation (columns 12-13; bridging paragraph). Applicants respectfully traverse this rejection.

Independent claim 74 has been amended to recite "wherein said cell cycle blocking agent is selected from the group consisting of taxol, taxolene, and a vinca alkaloid."

As discussed above, Son *et al.* and Roth *et al.*, alone or in combination, fail to disclose all of the elements of the claimed invention. Moreover, as discussed in detail above, Son *et al.* teach away from the claimed invention. Therefore, one of skill in the art would not have been motivated to combine Son *et al.* and Roth *et al.* Bally *et al.* fail to cure this deficiency. Bally *et al.* does not disclose the use of a claimed cell cycle blocking agent: taxol, taxolene, vinblastine, vincristine, vinorelbine, and a vinca alkaloid. Moreover, there is no hint or suggestion in Bally *et al.* of the use of a cell cycle blocking agent. Therefore, one of skill in the art would not have had the motivation to combine Bally *et al.* with Son *et al.* and Roth *et al.* Even if one of skill in the art were to combine Son *et al.*, Roth *et al.*, and Bally, *et al.*, the combination would not lead to the claimed invention because none of the references alone, or in combination teach or suggest the use of the cell cycle blocking agents of the claimed invention.

Absent a teaching or suggestion of the use of cell cycle blockers as disclosed and claimed in the present invention, the present invention is non-obvious, and thus, patentable. Accordingly, Applicants respectfully request withdrawal of this rejection.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is urged. If the Examiner believes a telephone conference would aid in the prosecution of this case in any way, please call the undersigned at 415-576-0200.

Respectfully submitted,

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APPENDIX A

38. (Twice Amended) A method of introducing a nucleic acid comprising [enhancing the therapeutic effect of] a foreign therapeutic gene into a cell in [administered to] a patient, said method comprising the steps of

(a) administering a cell cycle blocking agent to said patient, wherein said cell cycle blocking agent is a member selected from the group consisting of taxol, taxolene, and a vinca alkaloid; and

(b) administering said nucleic acid [foreign therapeutic gene] to said patient within seven days of step (a)[, wherein said foreign therapeutic gene is fully encapsulated in a lipid formulation such that less than 5% of the gene is degraded after exposure of said formulation to 1 U DNAse I for 30 minutes in digestion buffer at 37°C].

47. (Once Amended) The method of claim 38, wherein said cell cycle blocking agent is selected from the group consisting of cyclophosphamide, [etoposide,] taxol, and vincristine[,cisplatin, doxorubicin, and 5-flouracil].

69. (Once Amended) A method of inhibiting growth of cancer cells in a patient having a cancer comprising introducing a nucleic acid comprising a foreign therapeutic gene into a cell in [enhancing the therapeutic effect of a foreign therapeutic gene administered to] a patient having cancer, said method comprising the steps of:

(a) administering a cell cycle blocking agent to said patient, wherein said cell cycle blocking agent is a member selected from the group consisting of taxol, taxolene, and a vinca alkaloid; and

(b) administering said nucleic acid [foreign therapeutic gene] to said patient within seven days of step (a), wherein said nucleic acid [foreign therapeutic gene] is administered systemically.

74. (Once Amended) A method of treating a patient having a cancer comprising introducing a nucleic acid comprising a foreign therapeutic gene into a cell in said patient [enhancing the therapeutic effect of a foreign therapeutic gene administered to a patient], said method comprising the steps of:

(a) administering a cell cycle blocking agent to said patient, wherein said cell cycle blocking agent is a member selected from the group consisting of taxol, taxolene, and a vinca alkaloid; and

(b) administering said nucleic acid [foreign therapeutic gene] to said patient within seven days of step (a), wherein said nucleic acid [foreign therapeutic gene] is administered in a lipid formulation comprising a cationic lipid and a lipid derivative selected from the group consisting of an ATTA-lipid, a polyethylene glycol (PEG)-lipid derivative, and a ganglioside G_{M1}-modified lipid,

wherein said nucleic acid is fully encapsulated in said lipid formulation such that less than 5% of the nucleic acid is degraded after exposure of said formulation to 1 U DNAse I for 30 minutes in digestion buffer at 37°C.

77. (Once Amended) The method of claim 74, wherein said lipid derivative is present in an amount of from about 1% to about 20% by weight of the lipid formulation.

78. (New) The method of claim 74 , wherein said lipid formulation is prepared by the method comprising:

(a) contacting said nucleic acid with a solution comprising non-cationic lipids and a detergent to form a nucleic acid-lipid mixture;

(b) contacting said cationic lipid with the nucleic acid-lipid mixture, thereby forming a charge-neutralized mixture of nucleic acids and lipids; and

(c) removing the detergent from the charge-neutralized mixture to provide the lipid-nucleic acid particles in which the nucleic acids are protected from degradation.

79. (New) The method of claim 38, wherein the vinca alkaloid is a member selected from the group consisting of vinblastine, vincristine, and vinorelbine.

80. (New) The method of claim 38, wherein the nucleic acid is in a lipid formulation.

81. (New) The method of claim 80, wherein the nucleic acid is fully encapsulated in a lipid formulation such that less than 5% of the nucleic acid is degraded after exposure of said formulation to 1 U DNAse I for 30 minutes in digestion buffer at 37°C.

82. (New) The method of claim 80, wherein said lipid formulation is prepared by the method comprising:

(a) contacting said nucleic acid with a solution comprising non-cationic lipids and a detergent to form a nucleic acid-lipid mixture;

(b) contacting cationic lipids with the nucleic acid-lipid mixture, thereby forming a charge-neutralized mixture of nucleic acids and lipids; and

(c) removing the detergent from the charge-neutralized mixture to provide the lipid-nucleic acid particles in which the nucleic acids are protected from degradation.

83. (New) The method of claim 69, wherein the vinca alkaloid is a member selected from the group consisting of vinblastine, vincristine, and vinorelbine.

84. (New) The method of claim 74, wherein the vinca alkaloid is a member selected from the group consisting of vinblastine, vincristine, and vinorelbine.

APPENDIX B

PENDING CLAIMS SUBJECT TO EXAMINATION

38. (Twice Amended) A method of introducing a nucleic acid into a cell in a patient, said method comprising the steps of

(a) administering a cell cycle blocking agent to said patient, wherein said cell cycle blocking agent is a member selected from the group consisting of taxol, taxolene, and a vinca alkaloid; and

(b) administering said nucleic acid to said patient within seven days of step (a).

39. (As filed) The method of claim 38 wherein step (b) is performed within 3 days of step (a)

40. (As filed) The method of claim 38 wherein step (b) is performed within 24 hours of step (a).

41. (As filed) The method of claim 38 wherein said foreign therapeutic gene is a plasmid.

42. (As filed) The method of claim 38 wherein said foreign therapeutic gene comprises a gene selected from the group consisting of genes encoding a cytokine, apoptotic protein, tumor suppressor, heat shock protein, immunogenic antigen, proteinase inhibitor, anti-angiogenic protein, suicide gene for use in GDEPT, ribozyme, antisense nucleic acid, viral protein and a toxin.

43. (As filed) The method of claim 38 wherein said foreign therapeutic gene is administered systemically.

44. (As filed) The method of claim 38 wherein said foreign therapeutic gene is administered locally or regionally.

46. (As filed) The method of claim 38 wherein said cell cycle blocking agent is selected from the group consisting of DNA alkylating agents, DNA topoisomerase inhibitors, microtubule assembly inhibitors, microtubule disassembly inhibitors, DNA-cross linking agents, DNA-binding agents and nucleoside analogues.

47. (Once Amended) The method of claim 38, wherein said cell cycle blocking agent is selected from the group consisting of cyclophosphamide, taxol, and vincristine.

48. (As filed) The method of claim 38 wherein said cell cycle blocking agent is in a liposome formulation.

49. (As filed) A method of claim 38 wherein said cell cycle blocking agent is administered prior to administering said foreign therapeutic gene.

50. (As filed) A method of claim 38 wherein said cell cycle blocking agent is administered at least 32 h prior to administering said foreign therapeutic gene.

51. (As filed) A method of claim 38 wherein said cell cycle blocking agent is administered at least 48 h prior to administering said foreign therapeutic gene.

52. (As filed) A method of claim 38 wherein said foreign therapeutic gene is administered prior to administering said cell cycle blocking agent.

53. (As filed) A method of claim 38 wherein said foreign therapeutic gene is administered at least 32 h prior to administering said cell cycle blocking agent.

54. (As filed) A method of claim 38 wherein said foreign therapeutic gene is administered at least 48 h prior to administering said cell cycle blocking agent.

69. (Once Amended) A method of inhibiting growth of cancer cells in a patient having a cancer comprising introducing a nucleic acid comprising a foreign therapeutic gene into a cell in a patient having cancer, said method comprising the steps of:

(a) administering a cell cycle blocking agent to said patient, wherein said cell cycle blocking agent is a member selected from the group consisting of taxol, taxolene, and a vinca alkaloid; and

(b) administering said nucleic acid to said patient within seven days of step (a), wherein said nucleic acid is administered systemically.

70. (As filed) The method of claim 69, wherein said cancer comprises a tumor.

71. (As filed) The method of claim 70, wherein said cell cycle blocking agent and said foreign therapeutic gene are administered distal to the site of the tumor.

72. (As filed) The method of claim 69, wherein said cell cycle blocking agent or said foreign therapeutic gene are administered intravenously.

73. (As filed) The method of claim 69, wherein said cell cycle blocking agent or said foreign therapeutic gene are administered intraperitoneally.

74. (Once Amended) A method of treating a patient having a cancer comprising introducing a nucleic acid comprising a foreign therapeutic gene into a cell in said patient, said method comprising the steps of:

(a) administering a cell cycle blocking agent to said patient, wherein said cell cycle blocking agent is a member selected from the group consisting of taxol, taxolene, and a vinca alkaloid; and

(b) administering said nucleic acid to said patient within seven days of step (a), wherein said nucleic acid is administered in a lipid formulation comprising a cationic lipid and a lipid derivative selected from the group consisting of an ATTA-lipid, a polyethylene glycol (PEG)-lipid derivative, and a ganglioside G_{M1}-modified lipid,

wherein said nucleic acid is fully encapsulated in said lipid formulation such that less than 5% of the nucleic acid is degraded after exposure of said formulation to 1 U DNAse I for 30 minutes in digestion buffer at 37°C.

75. (As filed) The method of claim 74, wherein said (PEG)-lipid derivative is a PEG-ceramide.

76. (As filed) The method of claim 75, wherein said PEG-ceramide is a member selected from the group of PEG-Cer-C14, PEG-Cer-C20, and PEG-Cer-C8.

77. (Once Amended) The method of claim 74, wherein said lipid derivative is present in an amount of from about 1% to about 20% by weight of the lipid formulation.

78. (New) The method of claim 74, wherein said lipid formulation is prepared by the method comprising:

(a) contacting said nucleic acid with a solution comprising non-cationic lipids and a detergent to form a nucleic acid-lipid mixture;

(b) contacting said cationic lipid with the nucleic acid-lipid mixture, thereby forming a charge-neutralized mixture of nucleic acids and lipids; and

(c) removing the detergent from the charge-neutralized mixture to provide the lipid-nucleic acid particles in which the nucleic acids are protected from degradation.

79. (New) The method of claim 38, wherein the vinca alkaloid is a member selected from the group consisting of vinblastine, vincristine, and vinorelbine.

80. (New) The method of claim 38, wherein the nucleic acid is in a lipid formulation.

81. (New) The method of claim 80, wherein the nucleic acid is fully encapsulated in a lipid formulation such that less than 5% of the nucleic acid is degraded after exposure of said formulation to 1 U DNAse I for 30 minutes in digestion buffer at 37°C.

82. (New) The method of claim 80, wherein said lipid formulation is prepared by the method comprising:

(a) contacting said nucleic acid with a solution comprising non-cationic lipids and a detergent to form a nucleic acid-lipid mixture;

(b) contacting cationic lipids with the nucleic acid-lipid mixture, thereby forming a charge-neutralized mixture of nucleic acids and lipids; and

(c) removing the detergent from the charge-neutralized mixture to provide the lipid-nucleic acid particles in which the nucleic acids are protected from degradation.

83. (New) The method of claim 69, wherein the vinca alkaloid is a member selected from the group consisting of vinblastine, vincristine, and vinorelbine.

84. (New) The method of claim 74, wherein the vinca alkaloid is a member selected from the group consisting of vinblastine, vincristine, and vinorelbine.